

What is claimed is:

1. An isolated nucleic acid sequence encoding a polypeptide, wherein the polypeptide is selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL).
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2. The nucleic acid sequence of Claim 1, which is DNA or RNA.
3. The nucleic acid sequence of Claim 1, comprising a nucleotide sequence
10 selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20.
4. The nucleic acid sequence of Claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 5, 6, 8, 10, 12, 14, 16, 19, 21, and 70.
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5. The nucleic acid sequence of Claim 1, which encodes human PSF.
6. An isolated nucleic acid sequence that hybridizes under high-stringency conditions to a second nucleic acid sequence, wherein the second nucleic acid is
20 complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20, or to a continuous fragment thereof.
7. A purified polypeptide, selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL).
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8. The polypeptide of Claim 7, comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 5, 6, 8, 10, 12, 14, 16, 19, 21, and 70.
9. The polypeptide of Claim 7, which is encoded by a nucleotide sequence
30 selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20.
10. The polypeptide of Claim 7, which is human PSF.

11. A purified polypeptide encoded by a nucleic acid sequence that hybridizes under high-stringency conditions to a second nucleic acid sequence, wherein the second nucleic acid sequence is complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20, or to a continuous
5 fragment thereof.

12. A pharmaceutical composition, comprising a pharmaceutically-acceptable carrier and presenilin stabilization factor (PSF) or presenilin stabilization factor-like protein (PSFL).
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13. An antibody specific for a polypeptide, wherein the polypeptide is selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL).
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14. The antibody of Claim 13, wherein the polypeptide is human PSF.

15. A method for producing an antibody specific for a polypeptide selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL), comprising the steps of:
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- (a) immunizing a mammal with the selected polypeptide; and
- (b) purifying antibody from a tissue of the mammal or from a hybridoma made using tissue of the mammal.

16. The method of Claim 15, wherein the polypeptide is human PSF.
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17. An antibody produced by the method of Claim 15.

18. A vector comprising a nucleic acid sequence encoding a polypeptide, wherein the polypeptide is selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL).
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19. The vector of Claim 18, wherein the nucleic acid sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20.

20. The vector of Claim 18, wherein the nucleic acid sequence hybridizes under high-stringency conditions to a second nucleic acid sequence, wherein the second nucleic acid sequence is complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 7, 9, 11, 13, 15, 17, 18, and 20, or to a continuous fragment thereof.

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21. The vector of Claim 18, wherein the nucleic acid sequence encodes human PSF.

22. A host cell transformed with the vector of Claim 18.

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23. A transgenic animal containing the host cell of Claim 22.

24. A method for making a polypeptide selected from the group consisting of presenilin stabilization factor (PSF) and PSF-like protein (PSFL), comprising the steps of:

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(a) introducing into a host cell a nucleic acid sequence encoding the selected polypeptide;

(b) maintaining the host cell under conditions such that the nucleic acid sequence is expressed to produce the selected polypeptide; and

(c) recovering the selected polypeptide.

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25. The method of Claim 24, wherein the polypeptide is human PSF.

26. A method for decreasing amyloid-beta production in a cell, comprising decreasing activity of a presenilin-stabilizing molecule in the cell, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

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27. The method of Claim 26, wherein the molecule decreases amyloid-beta production in the cell by a biological process selected from the group consisting of:

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(a) destabilizing presenilin or nicastrin in the cell;

(b) destabilizing a gamma-secretase complex in the cell; and

(c) inhibiting activity of gamma-secretase in the cell.

28. The method of Claim 26, wherein activity of the molecule is decreased in the cell by contacting the cell with an inhibitor of the molecule.

29. The method of Claim 28, wherein the cell is contacted with an amount of the inhibitor effective to decrease amyloid-beta production in the cell.

30. The method of Claim 28, wherein the inhibitor is dsRNA.

31. The method of Claim 28, wherein the contacting is effected *in vitro*.

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32. The method of Claim 28, wherein the contacting is effected *in vivo* in a subject.

33. The method of Claim 32, wherein the contacting is effected *in vivo* in a subject by administering the inhibitor to the subject.

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34. The method of Claim 33, wherein the inhibitor is administered to the subject by introducing the inhibitor into cells of the subject.

35. The method of Claim 34, wherein the inhibitor is introduced into cells of the subject by a method selected from the group consisting of electroporation, DEAE Dextran transfection, calcium phosphate transfection, cationic liposome fusion, protoplast fusion, creation of an *in vivo* electrical field, DNA-coated microprojectile bombardment, injection with recombinant replication-defective viruses, homologous recombination, *in vivo* gene therapy, *ex vivo* gene therapy, viral vectors, and naked DNA transfer.

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36. The method of Claim 33, wherein the inhibitor is administered to the subject by oral administration, parenteral administration, transdermal administration, or osmotic pump.

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37. The method of Claim 32, wherein the subject is a human.

38. The method of Claim 37, wherein the human has neurodegeneration.

39. The method of Claim 38, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLHD), frontotemporal dementia (FTD), Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

40. The method of Claim 39, wherein the neurodegeneration is Alzheimer's disease.

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41. The method of Claim 40, wherein the Alzheimer's disease is early-onset familial Alzheimer's disease.

42. A pharmaceutical composition for decreasing amyloid-beta production, comprising a pharmaceutically-acceptable carrier and an inhibitor of a presenilin-stabilizing molecule, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

43. A method for destabilizing presenilin or nicastrin in a cell, comprising decreasing activity of a presenilin-stabilizing molecule in the cell, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

44. A method for destabilizing a gamma-secretase complex in a cell, comprising decreasing activity of a presenilin-stabilizing molecule in the cell, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

45. A method for inhibiting activity of gamma-secretase in a cell, comprising decreasing activity of a presenilin-stabilizing molecule in the cell, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

46. A method for decreasing amyloid-beta production in a cell, comprising increasing activity of a rhomboid peptide in the cell, wherein the peptide is selected from the group consisting of rhomboid 1 and rhomboid 7.

5 47. The method of Claim 46, wherein activity of the peptide is increased in the cell by contacting the cell with the peptide or a modulator of the peptide's expression.

48. The method of Claim 47, wherein the cell is contacted with an amount of the peptide or modulator effective to decrease amyloid-beta production in the cell.

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49. The method of Claim 47, wherein the contacting is effected *in vitro*.

50. The method of Claim 47, wherein the contacting is effected *in vivo* in a subject.

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51. The method of Claim 50, wherein the contacting is effected *in vivo* in a subject by administering the peptide or the modulator to the subject.

20 52. The method of Claim 51, wherein the peptide or the modulator is administered to the subject by oral administration, parenteral administration, transdermal administration, or osmotic pump.

25 53. The method of Claim 51, wherein the peptide or the modulator is administered to the subject by introducing a nucleic acid encoding the peptide or the modulator into cells of the subject, in a manner permitting expression of the peptide or the modulator.

30 54. The method of Claim 53, wherein the nucleic acid is introduced into cells of the subject by a method selected from the group consisting of electroporation, DEAE Dextran transfection, calcium phosphate transfection, cationic liposome fusion, protoplast fusion, creation of an *in vivo* electrical field, DNA-coated microprojectile bombardment, injection with recombinant replication-defective viruses, homologous recombination, *in vivo* gene therapy, *ex vivo* gene therapy, viral vectors, and naked DNA transfer.

55. The method of Claim 50, wherein the subject is a human.

56. The method of Claim 55, wherein the human has neurodegeneration.

57. The method of Claim 56, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLBH), frontotemporal dementia (FTD), Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

58. The method of Claim 57, wherein the neurodegeneration is Alzheimer's disease.

59. The method of Claim 58, wherein the Alzheimer's disease is early-onset familial Alzheimer's disease.

60. A pharmaceutical composition for decreasing amyloid-beta production, comprising a rhomboid peptide, or a modulator of the peptide's expression, and a pharmaceutically-acceptable carrier, wherein the peptide is selected from the group consisting of rhomboid 1 and rhomboid 7.

61. A method for treating neurodegeneration in a subject in need of treatment, comprising administering to the subject an inhibitor of a presenilin-stabilizing molecule, in an amount effective to treat the neurodegeneration, wherein the molecule is selected from the group consisting of presenilin stabilization factor (PSF) and presenilin stabilization factor-like protein (PSFL).

62. The method of Claim 61, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLBH), frontotemporal dementia (FTD), Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

63. The method of Claim 62, wherein the neurodegeneration is Alzheimer's disease.

64. The method of Claim 63, wherein the Alzheimer's disease is early-onset
5 familial Alzheimer's disease.

65. The method of Claim 61, wherein the inhibitor is dsRNA.

66. The method of Claim 61, wherein the inhibitor is administered to the subject
10 by introducing the inhibitor into cells of the subject.

67. The method of Claim 66, wherein the inhibitor is introduced into cells of the subject by a method selected from the group consisting of electroporation, DEAE Dextran transfection, calcium phosphate transfection, cationic liposome fusion, protoplast fusion,
15 creation of an *in vivo* electrical field, DNA-coated microprojectile bombardment, injection with recombinant replication-defective viruses, homologous recombination, *in vivo* gene therapy, *ex vivo* gene therapy, viral vectors, and naked DNA transfer.

68. A method for treating neurodegeneration in a subject in need of treatment,
20 comprising administering to the subject a rhomboid peptide, or a modulator of the peptide's expression, in an amount effective to treat the neurodegeneration, wherein the peptide is selected from the group consisting of rhomboid 1 and rhomboid 7.

69. The method of Claim 68, wherein the neurodegeneration is selected from the
25 group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLDH), frontotemporal dementia (FTD), Huntington's chorea, multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

30 70. The method of Claim 68, wherein the neurodegeneration is Alzheimer's disease.

71. The method of Claim 70, wherein the Alzheimer's disease is early-onset familial Alzheimer's disease.

5 72. The method of Claim 68, wherein the peptide or the modulator is administered to the subject by oral administration, parenteral administration, transdermal administration, or osmotic pump.

10 73. The method of Claim 68, wherein the peptide or the modulator is administered to the subject by introducing a nucleic acid encoding the peptide or the modulator into cells of the subject, in a manner permitting expression of the peptide or the modulator.

15 74. The method of Claim 73, wherein the nucleic acid is introduced into cells of the subject by a method selected from the group consisting of electroporation, DEAE Dextran transfection, calcium phosphate transfection, cationic liposome fusion, protoplast fusion, creation of an *in vivo* electrical field, DNA-coated microprojectile bombardment, injection with recombinant replication-defective viruses, homologous recombination, *in vivo* gene therapy, *ex vivo* gene therapy, viral vectors, and naked DNA transfer.

20 75. An *in vitro* system for identifying an agent that selectively modulates production of amyloid-beta or an amyloid-beta precursor, comprising *Drosophila*-derived S2 cells that express human APP, a human APP derivative, or a human presenilin.

25 76. A method for making an *in vitro* system for identifying an agent that selectively modulates production of amyloid-beta or an amyloid-beta precursor, comprising the step of:

(a) generating *Drosophila*-derived S2 cells that express human APP, a human APP derivative, or a human presenilin.

30 77. An *in vitro* system made by the method of Claim 76.

78. The *in vitro* system of Claim 77, wherein the method further comprises the steps of:

(b) contacting the cells with dsRNA for a candidate protein product; and

(c) assessing the ability of the dsRNA to modulate production of amyloid-beta or an amyloid-beta precursor in the cells, wherein ability of the dsRNA to modulate production of amyloid-beta or an amyloid-beta precursor is indicative that the candidate protein product modulates production of amyloid-beta or an amyloid-beta precursor.

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79. The *in vitro* system of Claim 77, wherein the method further comprises the steps of:

(b) contacting the cells with a candidate agent; and

(c) assessing the ability of the candidate agent to modulate production of amyloid-beta or an amyloid-beta precursor in the cells.

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80. A method for identifying a protein product that modulates production of amyloid-beta or an amyloid-beta precursor, comprising the steps of:

(a) obtaining or generating *Drosophila*-derived S2 cells that express human APP, a human APP derivative, or a human presenilin;

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(b) contacting the cells with dsRNA for a candidate protein product; and

(c) assessing the ability of the dsRNA to modulate production of amyloid-beta or an amyloid-beta precursor in the cells, wherein ability of the dsRNA to modulate production of amyloid-beta or an amyloid-beta precursor is indicative that the candidate protein product modulates production of amyloid-beta or an amyloid-beta precursor.

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81. A protein product identified by the method of Claim 80.

82. The protein product of Claim 81, which decreases production of amyloid-beta or an amyloid-beta precursor.

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83. A method for treating neurodegeneration in a subject in need of treatment, comprising administering to the subject an amount of the protein product of Claim 82 effective to treat neurodegeneration in the subject.

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84. The method of Claim 83, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLBH), frontotemporal dementia (FTD), Huntington's chorea,

multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

5 85. The method of Claim 84, wherein the neurodegeneration is Alzheimer's disease.

 86. The method of Claim 85, wherein the Alzheimer's disease is early-onset familial Alzheimer's disease.

10 87. A method for identifying an agent that modulates production of amyloid-beta or an amyloid-beta precursor, comprising the steps of:

- (a) obtaining or generating *Drosophila*-derived S2 cells that express human APP, a human APP derivative, or a human presenilin;
- (b) contacting the cells with a candidate agent; and
- 15 (c) assessing the ability of the candidate agent to modulate production of amyloid-beta or an amyloid-beta precursor in the cells.

 88. An agent identified by the method of Claim 87.

20 89. The agent of Claim 88, which decreases production of amyloid-beta.

 90. A method for treating neurodegeneration in a subject in need of treatment, comprising administering to the subject an amount of the agent of Claim 89 effective to treat neurodegeneration in the subject.

25 91. The method of Claim 90, wherein the neurodegeneration is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Binswanger's disease, corticobasal degeneration (CBD), dementia lacking distinctive histopathology (DLBH), frontotemporal dementia (FTD), Huntington's chorea,
30 multiple sclerosis, myasthenia gravis, Parkinson's disease, Pick's disease, and progressive supranuclear palsy (PSP).

 92. The method of Claim 91, wherein the neurodegeneration is Alzheimer's disease.

93. The method of Claim 92, wherein the Alzheimer's disease is early-onset familial Alzheimer's disease.